## REMARKS

Reconsideration of the present application in view of the following remarks is respectfully requested. Claims 1-8 are pending and are amended as provided herewith for clarity and to more particularly point out what applicants regard as the claimed invention; entry of these amendments is respectfully requested. Support for the amendments may be found in the specification, for example, at page 7, line 9 through page 8, line 14. No new subject matter has been added.

### DRAWINGS

The Action asserts that Figure 3 cannot be interpreted because groups 4 and 5 appear to be denoted with the same symbol and, therefore, corrected drawings are required. In response to this request, revised formal drawings (Figs. 1-3) are submitted herewith. No new subject matter has been added.

### REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner rejected claims 1-8 under 35 U.S.C. §112, second paragraph, as allegedly indefinite. More specifically, the Examiner is unclear regarding the meaning of "vaccine", and alleges that the word "vaccine" implies physiological protection against a disease or pathogen upon challenge with same. The Examiner also alleges that the meaning of "enhancing" is unclear.

Applicants respectfully traverse these grounds for rejection, and submit that the instant claims particularly point out and distinctly claim the subject matter which applicants regard as the invention, in compliance with the requirements of 35 U.S.C. §112, second paragraph. As disclosed in the specification (*e.g.*, page 7, line 9 through page 8, line 14) and recited in the claims, the present invention is directed in pertinent part to a cell surface receptor antigen vaccine for eliciting or enhancing the titer of antibodies specific for a cell surface receptor antigen, comprising one or more recombinant expression constructs comprising at least one promoter operably linked to a nucleic acid sequence encoding a cell surface receptor antigen (SRA) and a first and a second immune response altering molecule (IRAM). As described in the specification, for example, at page 2, line 25 through page 3, line 2; at page 5, line 21 through

page 7, line 8; at page 54, line 16 through page 56, line 12; and at page 57, line 20 through page 58, line 12; the invention relates to compositions that provide the unexpected advantage of eliciting sustained high titers of antibodies specific for a SRA.

Applicants respectfully submit that the meaning of "vaccine" is clear where the specification discloses, for example, at page 2, line 18 through page 3, line 2, the desirability of "the longer-lived protection afforded by a *vaccine, which influences the host immune state*" (emphasis added). Applicants submit further that, as disclosed in the specification, for example, at page 56, lines 9-12; and at page 57, line 20 through page 58, line 6; the subject invention SRA vaccine enhances (*e.g.,* significantly elevates) the titer of host antibodies specific for a cell SRA (*i.e.,* influences the host immune state) and also results in significantly reduced tumor cell growth *in vivo*. Therefore, contrary to the assertion in the Action, applicants respectfully submit that it is clear according to the instant application how "enhancing the titer of antibodies specific for a cell surface antigen" relates to a "vaccine", that is, a composition capable of influencing the host immune state by significantly elevating SRA-specific antibodies. As also described in the specification, a host immune state so altered may, for example, result in reduced tumor growth.

Moreover, applicants respectfully submit that those having ordinary skill in the art readily appreciate the meaning of "vaccine". As defined, for example, in *Dorland's Medical Dictionary* (28th Edition, 1994), a vaccine is "a suspension of attenuated or killed microorganisms, or of antigenic proteins derived from them, administered for the prevention, *amelioration, or* treatment of infectious diseases" (emphasis added). Applicants note further that *Dorland's* defines "amelioration" as "improvement, as of the condition of a patient". Accordingly, applicants submit that the Action is misguided in asserting that the specification does not teach protection where tumor growth in subjects immunized with a cell SRA vaccine occurs, albeit to a lesser degree than in subjects that are not immunized with a cell SRA vaccine according to the present invention. By way of contrast, applicants submit that a person having ordinary skill in the art would understand a vaccine to refer to a composition that may ameliorate disease, *i.e.,* that may improve the condition of the subject receiving the vaccine relative to a subject not receiving the vaccine. In other words, and in particular with reference to the use of the disjunctive "or" in the definition of "vaccine" above, applicants submit that a vaccine according to the present invention and as understood in the art can in fact ameliorate disease

(*e.g.*, retard tumor progression by reducing tumor growth, thereby improving the condition of a patient), even where tumor growth is not absolutely prevented. On this point applicants further respectfully submit that it is well known in the field of oncology to refer to an ameliorating treatment as one that significantly extends a patient's survival time, even where such treatment does not prevent disease or effect complete remission. Accordingly, applicants respectfully submit that the meaning of "vaccine" is clear.

Applicants also respectfully submit that the meaning of "enhancing" is clearly understood by persons having ordinary skill in the art, based upon the instant application. At page 49, lines 11-13, for example, the specification clearly teaches that the instant invention provides an enhanced humoral immune response such as generation of SRA specific antibody forming cells. Further teachings in the specification regarding such enhanced humoral responses may be found, for example, at page 6, line 26, through page 7, line 8; page 8, lines 15-17; and page 16, lines 12-15; including disclosure relating to induction of high and sustained titers of SRA specific antibodies. These teachings further include detection of such advantageously high antibody titers in a host treated with the subject invention vaccine, where such host would otherwise not be capable of such an immune response.

Well known methodologies for determining antibody titers are known in the art and are provided by the present specification, for example, at page 18, line 19 through page 19, line 12 (including references cited therein); at page 19, line 28 through page 20, line 6; and in Example 3. In this regard, applicants respectfully submit that according to these teachings (including the incorporated references), those having familiarity with the art are well aware that the state of the immunological arts appreciates the use of quantitative considerations for determining an antibody titer. Thus, for instance, the use of appropriate controls and statistical analysis of data to determine a meaningful level of enhancement, such as a statistically significant increase relative to a starting level, will be readily apparent to the skilled artisan based on the present application and the state of the art. Combined with an appreciation of the common meaning of "enhancing" as it may refer to raising or increasing in quantity, applicants therefore respectfully submit that a person having ordinary skill in the art would, given the present disclosure, discern no ambiguity in the recitation of this term in the instant claims.

Applicants therefore respectfully submit that the present application satisfies the requirements of 35 U.S.C. §112, second paragraph, and request that this basis for rejection be withdrawn.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH.

The Examiner also rejected claims 1-8 under 35 U.S.C. §112, first paragraph, for alleged lack of enabling support in the specification. In particular, the Action acknowledges that the specification enables individual expression constructs that recombinantly express Her2/neu, murine B7.2 or murine 4-1BB ligand, but asserts that the scope of the disclosure is not commensurate with the scope of *any* vaccine according to the claims. The Examiner cites Eck et al. (1996, *Gene Based Therapy*, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*-9th edition, McGraw-Hill, NY, pp. 77-101) in support of the assertion that numerous factors may complicate gene therapy in a manner that cannot be overcome by routine experimentation.

Applicants respectfully traverse these grounds for rejection and submit that the present application satisfies the requirements of 35 U.S.C. § 112, first paragraph. The specification clearly provides support for a wide variety of cell surface receptor antigen vaccines, including teachings directed to selection of suitable cell surface receptor antigens and immune response altering molecules (*e.g.*, page 8, line 15 through page 16, line 11; page 17, line 4 through page 18, line 15). Applicants respectfully submit that they are not required to specifically exemplify all embodiments of the invention that are encompassed by the claims. Instead, the requirements of 35 U.S.C. § 112, first paragraph, can be fulfilled by the use of illustrative examples or by broad terminology. *In re Anderson*, 176 U.S.P.Q. 331 (CCPA 1973). Applicants submit that they have met this requirement by teaching expression constructs that express Her2/neu, murine B7.1, murine B7.2 or murine 4-1BB ligand and demonstrating protection with vaccines comprising such recombinant expression constructs encoding a cell SRA (*e.g.*, Her2/neu) and a first and a second IRAM (*e.g.*, B7.1 and 4-1BB ligand, or B7.2 and 4-1BB ligand; see, *e.g.*, page 50, line 25 through page 58, line 12), as acknowledged in part by the Action. Furthermore, the Examiner has not pointed to any evidence that would lead a person having ordinary skill in the art to disbelieve the ability to use cell SRA vaccines of the current

invention to deliver other cell surface receptor antigens. Applicants therefore respectfully submit that, given the instant disclosure in view of the state of the art, an ordinarily skilled artisan would readily and without undue experimentation be able to make and use the SRA vaccines according to the instant claims.

With regard to the Examples, applicants respectfully wish to point out to the Examiner that the animals described in Example 2 of the application are not, in fact, nude mice, as alleged in the Action. The FVB/N-TgN (MMTVneu) mice are homozygous for the MMTVneu transgene and are viable and fertile, with spontaneous mammary tumors appearing in (female) animals of advanced age (*e.g.*, specification at page 53, lines 1-9). These mice provide a valuable animal model of human breast cancer caused by activation of the neu oncogene and are widely used and accepted in cancer and immunology research. Thus, applicants submit that data established in MMTVneu mice may, in fact, be extrapolated to humans and that the invention is fully enabled over the scope claimed.

Additionally with regard to the Examples, applicants respectfully submit that the observation regarding the host immune status of experimental Group 4 at page 7, paragraph 13 of the Action, is beside the point. As noted above, and as recited in the claims, the present invention is directed in pertinent part to a cell surface receptor antigen vaccine for eliciting or enhancing the titer of antibodies specific for a cell surface receptor antigen, comprising one or more recombinant expression constructs comprising at least one promoter operably linked to a nucleic acid sequence encoding a cell surface receptor antigen (SRA) and a first *and a second* immune response altering molecule (IRAM). Without prejudice to the filing of any future claims in the present application or in any divisional, continuation, continuation-in-part or other related application, the recombinant expression constructs provided to experimental Group 4 in the Examples of the instant application do not comprise a vaccine according to the present claims, where Group 4 received two recombinant expression constructs comprising at least one promoter operably linked to a nucleic acid sequence encoding a cell SRA and a first IRAM, but *not* a second IRAM. The present application discloses and, in fact, specifically points out the apparent down-regulation of immunological protection when the particular combination of the SRA (Her2/Neu) and the first IRAM (B7.2) is administered, as noted in the specification, for example, at page 56, lines 5-9; and at page 58, lines 6-12. Furthermore, the application contemplates the

use of such a combination in a vaccine embodiment that might desirably ameliorate a disease state, not by eliciting or enhancing an SRA-specific antibody titer according to the vaccines of the instant claims, but by SRA-specific down-regulation of lymphocyte activation or other immunological suppression.

Additionally, for enablement purposes, applicants respectfully submit that a specification need not teach what is well known in the art. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). Moreover, some amount of experimentation is not fatal as long as the amount is not undue. *Id.* For the instant claims, applicants therefore submit that no undue experimentation is required, because the specification provides sufficient guidance to allow a person having ordinary skill in the art to make and use a cell SRA vaccine comprising one or more recombinant expression constructs comprising at least one promoter operably linked to a nucleic acid sequence encoding a cell surface receptor antigen (SRA) and a first and a second immune response altering molecule (IRAM). More specifically, throughout the specification there are provided details regarding how to construct such a vector or vehicle and how to effectively deliver a gene. Furthermore, and contrary to the assertions in the Action regarding lack of examples demonstrating therapeutic methods, applicants submit that there is no requirement that applicants provide data for every therapeutic method (see *Amgen v. Chugai and Genetics Institute*, 927 F.2d 1200 (Fed. Cir. 1991)). It is well established that examples are not required for an enabling disclosure. *In re Robins*, 166 U.S.P.Q. 552 (C.C.P.A. 1970); *In re Borkowski*, 164 U.S.P.Q. 642 (C.C.P.A. 1970). The first paragraph of § 112 requires nothing more than objective enablement, which applicants have provided. In this regard, the PTO explicitly accepts the use of prophetic disclosures. Thus, the examples included in the present application should be considered as supportive of enablement, not as a detriment.

It is also respectfully submitted that a person having ordinary skill in the art of molecular biology can take any known protein encoding gene and place it in an expression vector with only routine, not undue, experimentation. Thus, the specification details a variety of vectors which may be desirable to deliver to cells, for example, at page 38, line 22 through page 44, line 14, including prokaryotic, eukaryotic and viral vectors, further including retroviral vectors. Further in this regard, applicants submit that the Action provides no basis whatsoever for its conclusion that undue experimentation would be required to provide a single recombinant

expression construct according to the claimed invention that comprises nucleic acid sequences encoding a cell SRA and a first and second IRAM. Applicants respectfully submit that nucleic acid vectors capable of expressing three proteins were available in the art at the time of filing. In addition and as noted above, the specification provides vectors, promoters, and other elements suitable for producing such an expression construct without undue experimentation. Clearly, the expression of multiple gene products from a single construct (*e.g.,* pMG, Virogene, Inc., San Diego, CA) is routine in the art. Other vectors containing bidirectional promoters and bicistronic expression vectors are commercially available (*e.g.,* pB1-EGFP and IRES, Clontech, Palo Alto, CA). On this point, applicants also respectfully submit that, as provided in the specification and as discussed herein, a wide variety of expression vectors (and sources of such expression vectors, see, *e.g.,* specification at page 39, lines 7-14; page 40, lines 1-13) are known to the art, including vectors capable of supporting the expression of a cell SRA and a first and second IRAM. For example, expression vectors capable of accommodating large inserts encoding one or more genes of interest are described in Wang et al. (1997 *Gene Ther.* 4:1132); Pechan et al. (1996 *Hum. Gene Ther.* 7:2003); Sena-Esteves et al., (1999 *J. Virol.* 73:10426); Sclimenti et al. (1998 *Curr. Opin. Biotechnol.* 9:476); and Wang et al. (2000 *BioTechniques* 28:102). Therefore, contrary to the Examiner's assertion, the methods of the present invention are enabled for methods of delivering a variety of protein encoding genes.

With regard to gene therapy, applicants respectfully disagree with the Examiner's characterization of the predictability of gene therapy, and with the implied assertion in the Action that applicants must provide human gene therapy data. If this is true, the Examiner is asserting that the claimed invention lacks *in vivo* utility. Although this rejection is not made under 35 U.S.C. § 101, the legal standard to be applied is the same. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995, holding that where the Examiner rejected pharmaceutical compositions based on §112, a §101 rejection for lack of utility would also have been proper. *See also* "Legal Analysis Supporting Utility Examination Guidelines", 60 F.R. 36263, July 14, 1995.)

Applicants respectfully submit that this rejection is improper in view of the PTO Guidelines which indicate that if reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or

pharmacological utility for a compound, composition or process. In no case has a Federal court required an applicant to support an asserted utility with data from human clinical trials. Moreover, in *In re Brana*, the Federal Circuit emphatically rejected the PTO position that human clinical testing is necessary to establish practical utility for an antitumor agent. 51 F.3d 1560. Importantly, the court noted, citing *In re Krimmel*, 130 U.S.P.Q. 205 (C.C.P.A. 1961):

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, *even though it may eventually appear that the compound is without value in the treatment of humans.* (Emphasis added)

Here, the situation is analogous. The instant specification describes a method of effective gene delivery; whether the method will eventually have commercial value in the treatment of humans is not a relevant inquiry to determine patentability.

In further support of the contention that the claims are not enabled, the Examiner cites the Eck et al. reference, allegedly disclosing problems with gene therapy. While this reference represents sweeping generalizations of gene therapy, it tells only one side of the story. In this regard, to date there are dozens of clinical trials in the U.S., and many more around the world, that involve the use of gene therapy. It is wholly unfair to focus solely upon the technical hurdles faced by some in the field while ignoring the successes.

For example, applicants wish to draw the Examiner's attention to the results of gene therapy to treat severe combined immunodeficiency, as disclosed by Blaese et al. (*Science 270*:475-480 (1995). In this study, two children with a genetic defect in production of adenosine deaminase (ADA) were treated with a cloned ADA gene inserted into a retroviral vector. To this day both patients continue to display significant improvement in their immune system function. The results of this gene therapy treatment were markedly superior to those produced earlier by alternative treatment means.

In a cancer context, Roth et al. (*Nature Medicine 2*(9):985-991 (1996)) have shown that a recombinant retroviral vector targets tumor cells *in vivo*. Moreover, this vector, which encodes the tumor suppressor p53, provided a sufficient level of p53 expression such that

apoptosis, or programmed cell death, was triggered in these cells. Accordingly, retrovirus gene therapy was accomplished *in vivo*. More recently, Khuri et al. (*Nature Medicine* 6(8):879-885 (2000)) reported a successful gene therapy regimen in human cancer patients using ONYX-015, an oncolytic, chimeric group C adenovirus having a large deletion in the E1B gene.

With respect to X-linked severe combined immunodeficiency (*i.e.*, SCID-X1), Cavazzana-Calvo et al. (*Science 288*:669-672 (2000)), have demonstrated full correction of disease phenotype in patients treated by gene therapy protocols. Further, Kay *et al.* (*Nature Genetics 24*:257-261 (2000)) have demonstrated therapeutic efficacy in the treatment of Haemophilia B with AAV vectors carrying the gene that encodes factor IX.

Moreover, the successes of gene therapy are in no way limited to only these examples. According to a recent review article,

> Probably the most remarkable conclusion drawn from the human trials is that human gene transfer is indeed feasible ... [and] most studies have shown that genes can be transferred to humans whether the strategy is *ex vivo* or *in vivo*, and that all vector types function as intended. Taken together, the evidence is overwhelming, with successful human gene transfer having been demonstrated in 28 *ex vivo* and 10 *in vivo* studies. Crystal, *Science 270*:404, 405 (1995).

Applicants respectfully submit that in view of the foregoing, a therapeutic method of gene delivery is adequately enabled by the instant application. Accordingly, as gene therapy as a whole clearly evidences enablement, and as applicants have described similar transduction using known methodologies such as the retroviral vectors described in the Examples of the present application, applicants respectfully submit that the rejection of the claims under 35 U.S.C. § 112, first paragraph, has been overcome and request that it be withdrawn.

REJECTIONS UNDER 35 U.S.C. §103

Claims 1-8 also stand rejected under 35 U.S.C. §103 for alleged obviousness over Hoo (U.S. Patent No. 5,891,432), Gerstmayer et al. (1997 *J. Immunol.* 158:4584) and Goodwin et al. (1993 *Eur. J. Immunol.* 23:2631). More specifically, the Examiner asserts that Hoo teaches a pharmaceutical composition that can contain a B7-2 molecule, which composition comprises a nucleic acid sequence encoding Her2/neu that can be expressed in a vector controlled by a CMV promoter. The Examiner then asserts that Gerstmayer et al. suggest that B7-2 molecules on tumor cell surfaces might be useful for cancer immunotherapy, and that Goodwin et al. teach 4-1BB ligand-mediated T cell stimulation and 4-1BB expression. The Examiner asserts further that a person having ordinary skill in the art would have been motivated to combine Hoo, Gerstmayer et al. and Goodwin et al. to arrive at the claimed invention.

Applicants respectfully traverse these grounds for rejection and submit that the claims are not obvious over the prior art, and further that the cited references, alone or in combination, fail to teach or suggest the claimed invention. The present invention is directed in pertinent part to a cell surface receptor antigen vaccine for eliciting or enhancing the titer of antibodies specific for a cell surface receptor antigen, comprising either (i) one or more recombinant expression constructs comprising at least one promoter operably linked to a nucleic acid sequence encoding a cell surface receptor antigen (SRA) and a first and a second immune response altering molecule (IRAM), or (ii) the expression products of such recombinant expression constructs. Applicants submit that the Examiner has not established a *prima facie* case of obviousness because the Action has not set forth sufficient evidence to show that at the time of filing the instant application, a person having ordinary skill in the art would have been motivated to combine the references in order to arrive at the claimed invention, with a reasonable expectation of success. In particular, and as discussed in greater detail below, the cited references fail to teach or suggest the claimed invention because they provide no motivation whatsoever to obtain a cell SRA vaccine according to the present invention, which vaccine elicits or enhances the titer of antibodies specific for a cell SRA, and which vaccine comprises at least one recombinant expression construct encoding a cell SRA and a first and a second IRAM, or the expression products of such recombinant expression constructs.

As described above, and as disclosed in the instant application, the vaccines of the present invention may be provided in the form of one or more recombinant expression constructs, or the expression products thereof. By way of contrast, Hoo provides a cell-based vaccine wherein the cell includes a fusion protein comprising a non-antibody immunomodulatory molecule domain (*e.g.*, GM-CSF) fused to a heterologous membrane attachment domain, and wherein the cell may further comprise a disease-associated antigen (*e.g.*, Her-2/neu) or an immunogenic portion thereof. Applicants respectfully submit that Hoo fails to disclose or suggest a cell surface receptor antigen vaccine for eliciting or enhancing the titer of SRA-specific antibodies according to the present invention comprising either (i) at least one recombinant expression construct that comprises, in pertinent part, a nucleic acid sequence encoding a cell SRA (*e.g.*, Her2/neu) as well as a first and a second IRAM, or (ii) the expression products thereof. Hoo merely describes transfection of a host cell that expresses a disease-associated antigen with a construct encoding a membrane-targeted immunomodulatory fusion protein, and the use of such a cell in a pharmaceutical composition. Moreover, applicants submit that Hoo teaches away from the present invention because Hoo is silent regarding whether any cell-based vaccine disclosed therein is capable of enhancing or eliciting the titer of antibodies specific for a cell surface receptor antigen, *i.e.*, in a cell surface receptor antigen-specific fashion.

Applicants therefore submit that neither the recombinant expression constructs (or combinations thereof) according to the claimed vaccines of the instant application, nor the expressed products thereof (also according to the instant claims) are contemplated by Hoo. Applicants are also somewhat confused by the assertion in the Action that the claims of Hoo teach a pharmaceutical composition comprising a nucleic acid sequence encoding Her2/neu, which teaching is not apparent to applicants in the absence of any reference by the Action to the specific claim(s) providing such teaching. Even assuming, *arguendo*, that such a teaching may be found in the claims of Hoo, applicants submit that Hoo still fails to teach or suggest a vaccine comprising the recombinant expression constructs of the present invention (or the expressed products thereof), nor does Hoo suggest a cell-based vaccine comprising the recombinant expression constructs (or combinations thereof) of the present invention. Additionally, applicants respectfully submit that the assertion in the Action is beside the point, regarding any teaching by Hoo of the optional inclusion of a B7-2 co-stimulatory molecule in cell-based

vaccines. Regardless of whether Hoo includes B7-2 in a vaccine, applicants submit that Hoo fails to provide or suggest the claimed invention cell SRA vaccine for eliciting or enhancing SRA-specific antibody titers. Hoo thus fails to suggest a vaccine comprising at least one recombinant expression vector encoding a cell SRA and a first and a second IRAM, or the expressed products thereof.

Furthermore, the deficiencies of Hoo are not remedied by Gerstmayer et al. or by Goodwin et al., alone or in combination. Applicants submit that the disclosures of Gerstmayer et al. and Goodwin et al. merely relate generally to compositions and methods for the expression of two particular examples of an IRAM as provided by the instant specification, and as known to the art. Applicants submit, however, that none of the cited references teach or in any way suggest the unexpected advantage provided by the subject invention vaccine as it relates to elicitation or enhancement of cell SRA-specific antibody titers by providing expression of a cell SRA and *two* IRAMs. Applicants therefore submit that the Examiner has not provided a case of *prima facie* obviousness, because the Action fails to point to any suggestion in the art that a vaccine for eliciting or enhancing SRA-specific antibodies should advantageously include expression constructs directing the expression of a cell SRA and *two* IRAMs (or expression products of such constructs). In fact, the introduction of Gerstmayer et al. (page 4584, left-hand column) and the discussion of Gerstmayer et al. (page 4587, Discussion, first paragraph) cite to numerous comparative analyses of B-7.1 and B-7.2 functions, but Gerstmayer et al. nowhere suggest any advantage associated with *combining* these two IRAMs in a vaccine for eliciting or enhancing cell SRA-specific antibodies. Gerstmayer et al. merely teach a construct expressing a chimeric fusion protein consisting of the extracellular domain of human B7-2 fused to a single-chain antibody domain specific for the ErbB2 protein.

Applicants submit further that the Action employs impermissible hindsight by invoking the provisions of MPEP section 2144.06 to allege that where the prior art teaches related functional effects of multiple immune response altering molecules when each is analyzed singly, it would have been obvious to combine any two such IRAMs to achieve the same functional effects. Applicants respectfully point out that the purposes of the prior art compositions are not the same where the art teaches that each IRAM mediates a unique function. Furthermore, the purpose of each prior art composition is *not* the same as the purpose of the

present invention, because the art fails to teach the purpose recited in the instant claims, namely, use of IRAMs in a cell SRA vaccine for eliciting or enhancing cell SRA-specific antibodies. In this context, the teachings of Hoo have already been discussed above. The teachings of Goodwin et al. relate to use of the 4-1BB ligand for the purpose of inducing proliferation, in a *non*-antigen-specific fashion, of mitogen-activated thymocytes and splenic T cells. Goodwin et al. speculate (page 2640, second complete paragraph) on the role of 4-1BB ligand as one of multiple mutually exclusive mediators of secondary T cell activation signals:

> It will be of interest to determine the precise role for *each* of these receptor-ligand interactions in an immune response and what *unique function they each may play*. (Goodwin et al., page 2640, emphasis added)

Accordingly, applicants submit that, if anything, a person having ordinary skill in the art would reasonably conclude, based on the disclosure of Goodwin et al., that different IRAMs mediate distinct immunological functions. Therefore, such an artisan would not have been motivated to combine 4-1BB, the IRAM of Goodwin et al. with IRAM from other references, with an expectation of successfully achieving the same purpose, when Goodwin et al. suggest that each IRAM may promote a unique and distinct function. Similarly, the teachings of Gerstmayer et al. relate to B7-2 promotion of *non*-antigen-specific, PMA-induced T cell proliferation as a model for cell-mediated tumor rejection with no suggestion of the desirability of eliciting or enhancing cell SRA-specific antibodies, and with no suggestion of advantageously combining B7-2 with any other IRAM. Thus, applicants respectfully submit that where, as here, the prior art fails to teach the usefulness of two compositions for the same purpose, the teachings of MPEP 2144.06 have been inappropriately applied.

Applicants therefore respectfully submit that the cited references lack any teaching with respect to induction of SRA-specific antibodies. As noted above, Hoo merely provides a whole-cell vaccine and is silent with respect to SRA-specific antibodies, disclosing only a prophetic example (Hoo, Column 26) describing how to detect antibodies that react with CT-26 cells but lacking any teaching directed to detection of antibodies specific for any particular cell SRA. The teachings of Gerstmayer et al. and of Goodwin et al. are limited to demonstration that, respectively, the IRAMs B7-2 and 4-1BB-ligand promote T cell proliferation

under appropriate conditions, without any demonstration of a role for either IRAM in eliciting or enhancing antibodies, and without any demonstration of a role for either IRAM in doing so in an antigen-specific manner (*i.e.,* induction of SRA-specific antibodies). Applicants therefore respectfully submit that a person having ordinary skill in the art would not have been motivated to combine Hoo, Gerstmayer et al. and Goodwin et al. to arrive at the presently claimed vaccine for eliciting or enhancing SRA-specific antibody titers, where such an artisan could not reasonably have concluded from these references that there could be *any* beneficial result from preparing a vaccine directed to a nominal antigen (SRA) with two IRAMs rather than one IRAM.

In view of the foregoing, Applicants submit that all of the claims are non-obvious in light of the cited references and request that the Examiner withdraw the rejection under 35 U.S.C. § 103.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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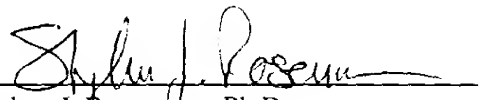

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Enclosures:

Postcard
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Form PTO-1083 (+ copy)
Petition for an Extension of Time (+ 2 copies)
Formal Drawings (Figs. 1-3)

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